

**Chief Editor's Note:** This article is the 28th of 36 that will be published in 2006 for which a total of up to 36 AMA PRA Category 1 Credits™ can be earned. Instructions for how credits can be earned precede the CME Examination at the back of this issue.

# Comparative Study of Thiazolidinediones in Clinical Use

W. Fernando Trigoso, MD

**Abstract:** Type 2 diabetes is a disease state associated with various metabolic abnormalities, including dyslipidemia and hypertension, which increase cardiovascular risks. Consequently, the goals for management of type 2 diabetes have evolved in recent years to include other measures aside from only glycemic control (eg, blood pressure, lipid levels). The thiazolidinediones (TZDs) play a fundamental role in the management of type 2 diabetes. These agents provide effective, lasting glycemic control and may exert beneficial effects on atherogenic processes. This retrospective database analysis was designed to evaluate the effects of rosiglitazone, pioglitazone, and troglitazone in the clinical practice setting. We conclude that the 3 TZDs are equally effective in maintaining glycemic control and have similar incidences of weight gain and edema in the long term. These agents may produce subtle variations in lipid profiles as described in short-term studies, but this is the first study that addresses the lipid data more than 1 year after treatment. Some subtle variations in blood pressure effects were noted demonstrating the need for fewer antihypertensive medications for patients taking rosiglitazone to achieve the same blood pressure goals as patients taking pioglitazone or troglitazone.

**Key Words:** thiazolidinediones, lipids, hypertension, comparative  
(*The Endocrinologist* 2006;16: 271–278)

## Learning Objectives

- Compare 3 thiazolidinedione (TZD) drugs for their efficacy in controlling hyperglycemia in patients with type 2 diabetes, as reflected by levels of glycosylated hemoglobin as

well as changes in the use of insulin, insulin secretagogues, and metformin.

- Contrast the 3 TZDs under study with respect to their effects on the lipid profile and blood pressure, and on requirements for the concomitant use of lipid-lowering and antihypertensive medications.
- Point out any differences between the 3 TZDs in the frequency of side effects.

Most patients with type 2 diabetes exhibit a cluster of abnormalities that include insulin resistance, dyslipidemia, and hypertension. These characteristics are associated with increased risk of cardiovascular disease. Consequently, the objectives for management of type 2 diabetes have been revised several times in recent years, changing from a focus on pure glycemic control to inclusion of goals intended to improve cardiovascular outcomes. Current guidelines from the American Diabetes Association (ADA) incorporate recommendations for the prevention and management of diabetic complications as well as the management of lipids, blood pressure, and nephropathy.<sup>1</sup>

The insulin-sensitizing thiazolidinediones (TZDs) play a fundamental role in the management of patients with type 2 diabetes. TZDs directly address the basic problem of insulin resistance by improving peripheral glucose disposal and insulin sensitivity in muscle, liver, and adipose tissue.<sup>2,3</sup> These agents effectively lower blood glucose levels in patients with type 2 diabetes<sup>4,5</sup> and may have beneficial effects on atherogenic processes within the vessel wall.<sup>6</sup> TZDs also appear to improve some aspects of dyslipidemia associated with type 2 diabetes.<sup>7</sup>

Rosiglitazone and pioglitazone are the 2 TZDs currently available in the United States; troglitazone was withdrawn from clinical use in March 2001 as the result of rare, but serious, drug-related hepatic failure. Comparisons of published clinical trial data suggest that the available TZDs have similar glycemic effects.<sup>4,5,8–27</sup> However, some studies intended to compare the effects of individual TZDs on lipid parameters have been plagued with bias and design errors and are usually too short in duration to determine long-term effects that would be observed with clinical use.<sup>28–37</sup> This has

Attending Endocrinologist, Diabetes & Glandular Disease Clinic of San Antonio, P.A.; Chairman, Departments of Medicine, Methodist Specialty and Transplant Hospital and Santa Rosa Northwest Hospital; and Clinical Assistant Professor, University of Texas Health Science Center, San Antonio, TX.

Dr. Trigoso has disclosed that he is/was a member of the speakers' bureau for Amylin, GlaxoSmithKline, and Auxilium.

Lippincott Continuing Medical Education Institute, Inc. has identified and resolved all faculty conflicts of interest regarding this educational activity.

Reprints: W. Fernando Trigoso, MD, Diabetes & Glandular Disease Clinic of San Antonio, PA, 5107 Medical Drive, San Antonio, TX 78229. E-mail: [frigoso@texas.net](mailto:frigoso@texas.net)

Copyright © 2006 by Lippincott Williams & Wilkins

ISSN: 1051-2144/06/1605-0271

DOI: 10.1097/01.ten.0000235175.59743.54

led to conflicting data that require rigorous appraisal and evaluation by the clinician to draw legitimate conclusions.

In this analysis, the long-term effects of rosiglitazone, pioglitazone, and troglitazone in patients with type 2 diabetes in a clinical practice setting are evaluated.

## METHODS

In this retrospective database analysis, rosiglitazone, pioglitazone, and troglitazone were compared with respect to their effects on glycemic control, lipid parameters, blood pressure, weight variation, edema, and liver function in patients with type 2 diabetes. Another end point of this study was to determine if the addition of antilipidemic and antihypertensive medications to existing TZD therapy resulted in any differences in achieving ADA standards. Data were retrieved from an extensive review of patient records at the Diabetes and Glandular Disease Clinic in San Antonio, Texas. Cases of all patients continuously taking a TZD initiated at the clinic for at least 300 days, but for no more than 900 days, were evaluated. The treatment duration was chosen so that patients would be on a TZD for a significant amount of time and be compared with patients on troglitazone. Cases in which patients were exposed to more than one TZD were excluded from the study. Patient data were extracted from a computerized medical recordkeeping system.

Glycosylated hemoglobin (A1c), blood pressure, and lipid measurements (ie, total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides), weight, edema, and aspartate aminotransferase (AST) were compared before and after the initiation of the respective TZD. Other parameters observed were changes in the therapeutic regimen, including the use of insulin and insulin secretagogues, lipid-lowering therapies, and antihypertensive medications. To establish a correlation among the dosing of multiple brands of medications, data were imputed as a percentage of the maximal dose of each medication at the time of observation. Data for insulin use were recorded as the total amount of units used by each patient regardless of the brand or analog of insulin.

One-way analysis of variance (ANOVA) and  $\chi^2$  analysis were used to address significant differences among groups of patients before TZD initiation. These data were compared for age, gender, race, weight, presenting comorbidities, amount of insulin used, and additional medications, including sulfonylureas, metformin, antihypertensives, and antilipidemic medications. Data were also compared for duration of TZD treatment, percentage maximal dose of TZD, and time since first diagnosis (duration of diabetes). Once treatment was initiated with a TZD, paired *t* test and  $\chi^2$  analyses were performed to compare data within each TZD group; ANOVA was used to compare data among rosiglitazone, pioglitazone, and troglitazone groups.

## RESULTS

Two hundred eighty-seven cases met study criteria and were included in this review: 98 patients treated with pioglitazone, 99 patients treated with rosiglitazone, and 90 patients previously treated with troglitazone. Patients who were treated with a TZD before coming to the clinic were purged from the analyses because their start dates were inaccurate.

Baseline demographic characteristics of the study population are shown in Table 1; there were no significant differences among the treatment groups at baseline. The mean age of the study population was between 57.8 and 59.3 years, and average duration of diabetes was between 10.0 and 11.6 years. No differences were noted in gender, racial distribution, other comorbidities, or antihypertensives used before treatment with TZDs among the 3 groups. The most predominantly observed comorbidities at baseline were dyslipidemia, hypertension, and coronary artery disease. The majority of patients were being treated with an antihypertensive medication before the addition of TZD therapy.

Table 2 demonstrates the average number of days that each patient was exposed to TZD therapy at the time of the analysis and the percentage of the maximal TZD dose that was prescribed. On average, patients taking troglitazone took a significantly higher percentage of the maximum dose compared with patients treated with rosiglitazone or pioglitazone (ANOVA = 0.013). There was no statistical difference in the percentage of maximum dose taken by patients treated with either rosiglitazone or pioglitazone. There also were no differences among the groups with respect to units of insulin used daily, percentage of the maximum dose of sulfonylurea prescribed, or the amount of metformin prescribed daily. It is important to note that if patients received no concomitant diabetes medication at baseline, their percentage of dose was entered as a zero and they were included in the analysis.

Baseline values for A1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and mean arterial blood pressure (MABP) before TZD initiation are shown in Table 3. The mean baseline A1c for the study population receiving pioglitazone (8.98%) was slightly higher than the rosiglitazone (8.85%) and troglitazone (8.55%) groups, but the difference was not significant. Significant reductions in A1c were seen in each of the 3 treatment groups before and after the initiation of TZD therapy (*t* test <.0001); however, there were no significant differences in A1c reduction among groups (ANOVA = 0.564) (Fig. 1). Although no differences were observed among groups with respect to lipid parameters at baseline, significant decreases were observed for total cholesterol, LDL, and triglycerides subsequent to TZD initiation in each treatment group (Table 4). A significant increase in HDL was seen only in patients receiving pioglitazone or rosiglitazone. Pioglitazone and rosiglitazone were statistically superior to troglitazone with respect to raising HDL. There were no statistical differences among the 3 drugs with regard to their effects on total cholesterol, LDL, or triglycerides.

Evaluations of antilipidemic medications prescribed concomitantly with individual TZD therapy were conducted. The mean percentage of maximum statin dosage was significantly higher after initiation of TZD therapy in each subset of patients (*t* test <.0001), increasing from 21.4% to 33.7% in the pioglitazone group, from 19.7% to 34.8% in the rosiglitazone group, and from 16.4% to 34% in the troglitazone group. The mean percentage of maximum fibrate dose increased from 70.9% to 71.9% in the pioglitazone group and from 78.5% to 85.1% in the rosiglitazone group and decreased from 64.1% to 57.7% in the troglitazone group. Comparing the TZDs with each

**TABLE 1.** Demographic Characteristics at Baseline

Demographic Characteristic	Pioglitazone (n = 98)	Rosiglitazone (n = 99)	Troglitazone (n = 90)	ANOVA or $\chi^2$
Age (yrs)				
Mean $\pm$ SD	57.8 $\pm$ 11.3	59.0 $\pm$ 13.4	59.3 $\pm$ 12.1	0.5746
Sex, n				0.7465
Male	52	55	45	
Female	46	44	45	
Duration of diabetes (yrs)				
Mean $\pm$ SD	10.7 $\pm$ 8.7	10.0 $\pm$ 8.2	11.6 $\pm$ 8.6	0.322
Racial distribution, n				0.4747
Asian	1	1	1	
Black	1	3	5	
Hispanic	46	54	50	
White	48	41	33	
Other	2	0	1	
Weight (lb)				
Mean $\pm$ SD	202.7 $\pm$ 46.8	196.9 $\pm$ 45.7	201.0 $\pm$ 44.7	0.647
Comorbidities, n				0.1917
Coronary artery disease	23	23	20	
Congestive heart failure	1	1	3	
Dyslipidemia	68	79	64	
Hypertension	56	72	65	
Other	123	94	82	
Antihypertensive therapy before treatment with TZD, n				0.7032
ACE inhibitor	42	41	37	
$\alpha$ -antagonist	2	2	3	
ARB	4	8	10	
$\beta$ -blocker	12	14	7	
Calcium channel blocker	16	18	19	

ACE indicates angiotensin-converting enzyme; ANOVA, one-way analysis of variance; ARB, angiotensin-receptor blocker; SD, standard deviation; TZD, thiazolidinedione.

**TABLE 2.** Thiazolidinedione Exposure and Concomitant Antidiabetic Medications

Baseline Characteristic	Pioglitazone (n = 98)	Rosiglitazone (n = 99)	Troglitazone (n = 90)	ANOVA
Duration of TZD exposure (days)				
Mean $\pm$ SD	528.7 $\pm$ 149.1	514.5 $\pm$ 154.8	547.8 $\pm$ 145.9	0.1979
Percentage maximal dose (%)				
Mean $\pm$ SD	76 $\pm$ 22	78 $\pm$ 28	86 $\pm$ 20	*
Concomitant antidiabetic medication use Insulin (units)				
Mean $\pm$ SD	63 $\pm$ 63.8	57.6 $\pm$ 25	61.2 $\pm$ 30.2	0.4876
Sulfonylurea (percent maximal dose)				
Mean $\pm$ SD	58 $\pm$ 27	50 $\pm$ 29	54 $\pm$ 30	0.2845
Metformin (mg)				
Mean $\pm$ SD	1829.7 $\pm$ 666.7	1888.7 $\pm$ 505.9	1829.7 $\pm$ 666.7	0.9996

\*ANOVA = 0.0130 for troglitazone versus pioglitazone and rosiglitazone; *t* test = 0.7067 for pioglitazone versus rosiglitazone. ANOVA indicates one-way analysis of variance; SD, standard deviation; TZD, thiazolidinedione.

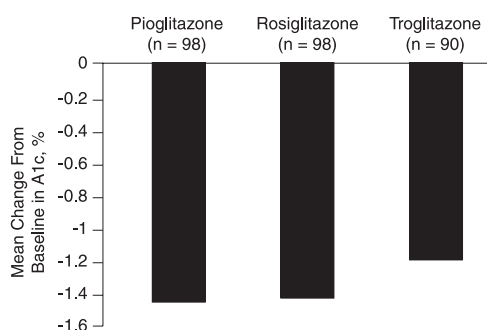
other showed no significant difference in the use of antilipidemic medications. There were no significant variations in the use of triglyceride-lowering medications within or among the 3 TZD groups. It is important to note that for patients who did not receive a statin at baseline, their percentage of dose was entered as a zero and they were included in the analysis.

Among insulin users, the number of units of insulin used daily decreased significantly in each group after TZD therapy was introduced, although no differences among the groups were observed. Similar analyses were performed to measure the use of insulin secretagogues before and after TZD initiation. The results were similar to those for insulin except that

**TABLE 3.** Glycemic, Blood Pressure, and Lipid Parameters at Baseline

Baseline Characteristic	Pioglitazone	Rosiglitazone	Troglitazone	ANOVA
A1c (%)				
Mean $\pm$ SD	8.98 $\pm$ 1.9	8.85 $\pm$ 2.1	8.55 $\pm$ 1.7	0.3847
MABP (mm Hg)				
Mean $\pm$ SD	94.9 $\pm$ 10.7	94.5 $\pm$ 12.8	97.4 $\pm$ 9.2	0.2752
Total cholesterol (mg/dL)				
Mean $\pm$ SD	192.4 $\pm$ 53.4	191.3 $\pm$ 40.4	202.7 $\pm$ 39.9	0.1279
LDL-C (mg/dL)				
Mean $\pm$ SD	109.9 $\pm$ 31.7	110.5 $\pm$ 31.6	116.5 $\pm$ 33.2	0.2450
HDL-C (mg/dL)				
Mean $\pm$ SD	44.8 $\pm$ 13.2	44.0 $\pm$ 11.6	47.9 $\pm$ 13.3	0.1610
Triglycerides (mg/dL)				
Mean $\pm$ SD	272.1 $\pm$ 474.1	281.6 $\pm$ 331.1	233.9 $\pm$ 183.2	0.462

A1c indicates glycosylated hemoglobin; ANOVA, one-way analysis of variance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MABP, mean arterial blood pressure; SD, standard deviation.



**FIGURE 1.** Mean change from baseline in A1c.\* Paired *t* test <.0001 for comparison before and after TZD treatment of all 3 treatment groups; ANOVA = 0.564 for between-group comparison. A1C indicates glycosylated hemoglobin; ANOVA, one-way analysis of variance; TZD, thiazolidinedione.

the decrease observed with pioglitazone did not reach statistical significance. There were no differences among the groups with respect to amount of metformin prescribed before and after the addition of TZD therapy.

A tendency toward decreasing MABP was observed in all treatment groups subsequent to the initiation of TZD therapy. A significant decrease was found only in the troglitazone group ( $P = 0.02$ ). In a separate analysis, a comparison was made among the 3 groups regarding the number of patients attaining the ADA criteria for target blood pressure (130/80 mm Hg). No significant difference was found among patients taking pioglitazone, rosiglitazone, or troglitazone, with 62.2%, 62.6%, and 54.6% of patients reaching the target ADA goal, respectively. Patients treated with pioglitazone (39.9% before and 53.1% after; *t* test = 0.0029) and troglitazone (36.3% before and 47.1% after; *t* test = 0.0211) demonstrated a significant increase in the mean percentage of maximal dose of antihypertensive used before and after TZD therapy. An increase in percentage of maximal dose was also observed in the rosiglitazone group (37.6% before and 40.1% after; *t* test = 0.2733), but did not reach statistical significance.

Patients receiving rosiglitazone used significantly fewer antihypertensive medications to reach similar ADA blood pressure goals compared with patients receiving the other 2 TZDs.

The classes of antihypertensive agents used by patients in each of the 3 groups were reviewed, and it was concluded that the observed difference in the percentage of maximum dose was not a result of the class proportions of antihypertensive used. In a review of the number of concomitant antihypertensive medications used per patient at baseline and after the initiation of TZD therapy, the percentage of patients using a single antihypertensive agent compared with patients using 2 agents did not change significantly in any group during the treatment period. The percentage of maximum dose was not a result of the use of a combination of antihypertensive agents or a single agent; no differences were observed among groups. In a similar analysis, the percentage of diuretics used in the pioglitazone and rosiglitazone groups increased significantly during the TZD treatment period. Further comparison among the groups did not show significant differences.

The incidence of commonly reported adverse events is summarized in Table 5. Incidence of subjectively reported weight gain was 20.4%, 17.2%, and 8.9% in the pioglitazone, rosiglitazone, and troglitazone groups, respectively, although no significant difference was observed among groups. There was no difference in the incidence of self-reported edema, hypoglycemia, dyspnea, or change in AST among groups.

## DISCUSSION

Based on the data from this study, rosiglitazone, pioglitazone, and troglitazone appear equally effective in lowering blood glucose levels in patients with type 2 diabetes and have similar incidences of weight gain and edema in the long term. However, in the evolution of type 2 diabetes management, it has become clear that glycemic control is not the only goal of treatment. Comorbid conditions such as hypercholesterolemia and hypertension also must be managed in these individuals. As a result, the ADA recommends that patients with diabetes be treated to a goal blood pressure of less than

**TABLE 4.** Lipid Parameters Before and After Thiazolidinedione Therapy

Treatment	Total Cholesterol (mg/dL)		LDL (mg/dL)		HDL (mg/dL)		Triglycerides (mg/dL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pioglitazone								
Before	192.4	53.4	109.9	31.7	44.8	13.2	272.1	474.1
After	180.9	48.6	98.6	27.8	49.4	12.9	204.7	255.4
<i>t</i> test	0.0144		0.0006		<0.0001		0.0015	
Rosiglitazone								
Before	191.3	40.4	110.5	31.6	44	11.6	281.6	331.1
After	182.6	35	103.8	26.9	47.9	11.9	205.3	225.1
<i>t</i> test	0.0138		0.0212		<0.0001		<0.0001	
Troglitazone								
Before	202.7	39.9	116.5	33.2	47.9	13.3	233.9	183.2
After	189.1	39.5	104.4	30.5	47.2	12.6	200	138.6
<i>t</i> test	0.0076		0.003		0.3137		0.0358	
ANOVA	0.38		0.4336		ANOVA <.0001 for pio and rosi versus tro		0.4467	
					<i>t</i> test = 0.8031 for pio versus rosi			

ANOVA indicates one-way analysis of variance; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; pio, pioglitazone; rosi, rosiglitazone; SD, standard deviation; tro, troglitazone.

**TABLE 5.** Incidence of Weight Gain, Edema, Hypoglycemia, Dyspnea, and Other Adverse Effects Reported by Patients During Treatment With Thiazolidinedione Therapy\*

Treatment	Incidence (%)				
	Weight Gain <sup>†</sup>	Edema	Hypoglycemia	Dyspnea	Other
Pioglitazone	20.4	19.4	2.0	0	5.1
Rosiglitazone	17.2	12.1	2.0	2.0	0
Troglitazone	8.9	11.1	0	0	0

\* $\chi^2$  analysis revealed no significant difference among groups ( $\chi^2 = 0.1608$ ).

<sup>†</sup>Subjectively reported weight gain.

130/80 mm Hg and lipid levels of LDL less than 100 mg/dL, triglycerides less than 150 mg/dL, and HDL greater than 40 mg/dL (American Diabetes Association, 2005); these guidelines are similar to those proposed for the general population by the National Cholesterol Education Program.<sup>38</sup>

As a result of heightened interest in modifying multiple risk factors simultaneously, a collection of data has accumulated comparing the effects of individual TZDs on cardiovascular outcomes. As a class, TZDs may improve some aspects of dyslipidemia associated with type 2 diabetes by increasing HDL, increasing LDL particle size, and possibly reducing triglycerides,<sup>7,22,34,39–44</sup> effects that may lead to improved cardiovascular outcomes. However, conflicting and inconsistent clinical trial reports have made it difficult for practitioners to draw accurate conclusions about the clinical significance of individual TZD effects, particularly with respect to LDL and triglycerides. Flaws in earlier studies with respect to trial design, marked differences in patient populations and baseline laboratory values, and short duration may account for disparities in findings.<sup>28–37</sup>

In this nonrandomized analysis, populations were carefully compared before the initiation of TZD therapy to ensure homogeneity and a high degree of validity. The duration of patient observation was also longer than in earlier studies and included a larger population. Based on findings from this study, it appears that TZDs may produce subtle variations in lipid profiles and blood pressure effects, but our overall analyses suggest that there are very few long-term differences among them. Results from this study demonstrated a significant decrease in triglycerides that was equally observed among the 3 TZDs evaluated. These results differ from comparisons made in earlier studies that were conducted during the acute phase of TZD initiation in smaller populations. In a retrospective study, triglyceride levels were found to have increased 13% with rosiglitazone but decreased 14% below baseline with pioglitazone (24% reduction overall,  $P = 0.02$ ). This study, however, only examined the charts of 20 patients and the duration of treatment was less than 1 year in all cases.<sup>36</sup> In addition, because the number of subjects in the study was small and the standard deviations were huge, the accuracy of the Student paired *t* test to determine significance is questionable.

Gegick and Altheimer<sup>32</sup> also reported notable triglyceride worsening when patients received rosiglitazone compared with pioglitazone, but their observational study was only 3.2 months in duration, and at the time that the new TZDs were initiated, more patients in the pioglitazone group (66%) were receiving statins versus the rosiglitazone group (48%). The researchers then performed a retrospective analysis to further address the change in lipids over time with the TZDs<sup>31</sup>; however, the study duration was only 12 months. Like in the previous study, more patients in the pioglitazone group (62.7%) were using statins versus patients in the rosiglitazone group (40.8%). Conversely, when Lewin and colleagues<sup>37</sup> studied the effects of simvastatin on the lipid profile

and attainment of LDL cholesterol goals when added to TZD therapy in patients with type 2 diabetes in a randomized, double-blind, placebo-controlled trial, it was unclear what the baseline lipids were for each group of patients (pioglitazone vs rosiglitazone). Nonetheless, the addition of simvastatin appeared to help them equally.

The consensus of the clinical literature that has drawn comparisons among TZDs seems to be that they are equal in their glucose-lowering ability and that individual selection may be based on other factors such as cardiovascular benefits and side effects. Unfortunately, the knowledge that we have attained in comparing individual TZDs is derived from earlier studies with very short durations involving small numbers of patients.<sup>28–37</sup> In an initial study comparing the efficacy and side effects of the 3 TZDs in the clinical practice setting, only 50 patients were included and the duration was 4 months.<sup>35</sup> Similarly, Davidson and colleagues<sup>29</sup> concluded in their randomized follow-up trial that pioglitazone appeared to be superior to both preceding troglitazone and alternative rosiglitazone therapy in improving A1c and dyslipidemia without significant weight gain. This study included only 39 patients. Faiman and colleagues<sup>30</sup> prospectively randomized 58 patients in their study that was 2 months in duration. This study suggested a trend toward lower triglyceride values in the pioglitazone group. In a retrospective review of randomly selected medical records, it was found that treatment with pioglitazone was associated with greater beneficial effects on blood lipid levels than treatment with rosiglitazone, but the average duration of treatment was only 17 weeks.<sup>28</sup> Data obtained from this study add to the existing collection of support for the effectiveness and safety of TZDs in lowering glucose levels but do not support the premise that large enough differences in cardiovascular effects exist to support clinical decision-making.

Appropriate study is critical for clinical conclusions, even if the population is large. A prospective, randomized study demonstrated significant improvement in the lipid profile after changing from troglitazone to pioglitazone versus rosiglitazone. The duration of treatment was again 4 months. The “washout” period from troglitazone was 2 weeks, and no prior data were given on how long patients were exposed to troglitazone before converting to rosiglitazone and pioglitazone. Also, the data on the use of metformin between groups were not clear.<sup>34</sup> Likewise, in a prospective, randomized study that demonstrated that pioglitazone compared with rosiglitazone is associated with a significant improvement in triglycerides, HDL cholesterol, LDL particle concentration, and LDL particle size, the patients were followed for 24 weeks.<sup>33</sup>

All of these studies end where our study begins. The data evaluated in prior studies compare baseline versus data less than 1 year into treatment. We compared data at baseline versus data more than 300 days after the initiation of treatment. Only the acute-phase effects are presented in these previous studies. By following the trends of all of these studies, it is clear that there is a tendency toward and dissipation of these differences over time. The larger number of cases in our analysis explains the contradictory information found in earlier TZD comparisons.

TZDs are not a substitute for conventional lipid-lowering therapies such as statins or fibrates in patients with type 2 diabetes. In this analysis, the observed lipid effects were likely the results of improved glycemic control combined with physician interventions to manage lipid levels. Patients were properly treated with antilipidemic therapy and managed according to ADA guidelines. This can be seen in the significant increase in statin use in all 3 treatment groups. Interventions with cholesterol-lowering medications were carefully evaluated, and there were no differences among the 3 groups in the amount of antilipidemic used. Based on this perspective, our study suggests that none of the TZDs opposed or restricted the action of antilipidemic medications. This finding is consistent with another randomized, double-blind study that demonstrated the addition of atorvastatin to rosiglitazone further improved lipid profiles in patients with type 2 diabetes.<sup>40</sup> Indeed, the majority of patients in our study achieved ADA lipid targets without compromise.

The prevalence of hypertension is up to 2 times greater in patients with diabetes than in patients without diabetes.<sup>45,46</sup> Hypertension is associated with substantial insulin resistance and, in the present study, TZD therapy with pioglitazone, rosiglitazone, and troglitazone were logically shown to reduce MABP. This is supported by similar findings in previously published trials.<sup>47–49</sup> In our analyses, a similar proportion of patients achieved the ADA-recommended target for blood pressure in each treatment group. Notably, patients receiving rosiglitazone required significantly fewer antihypertensive medications to reach this goal.

From our observations, we conclude that TZDs are equally effective in providing glycemic control (A1c) in patients with type 2 diabetes. These agents also appear to have similar effects on weight and edema. During the study, the majority of patients treated with TZDs reached target blood pressure goals as recommended by the ADA. Although small variations in lipid effects were noted with the TZDs evaluated, all 3 agents increased HDL and lowered triglyceride levels. Any differences in lipid-lowering ability diminished during the duration specified by this study. Additionally, none of the patients receiving TZDs required higher doses of statins or fibrates to achieve ADA lipid goals.

## ACKNOWLEDGMENTS

*Editorial assistance was underwritten by GlaxoSmith-Kline. The author gratefully acknowledges Virginia Schad of Scientific Therapeutics Information, Inc., Springfield, New Jersey, and thanks her for her editorial assistance in preparing the manuscript.*

## REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2005;28(suppl 1):S4–S6.
2. Kahn CR, Chen L, Cohen SE. Unraveling the mechanism of action of thiazolidinediones. *J Clin Invest*. 2000;106:1305–1307.
3. Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes*. 1996;45:1661–1669.
4. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL, the Pioglitazone 001 Study Group. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of

- patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. *Diabetes Care*. 2000;23:1605–1611.
5. Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI, for the Rosiglitazone Clinical Trials Study Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86:280–288.
  6. Dandona P, Aljada A. A rational approach to pathogenesis and treatment of type 2 diabetes mellitus, insulin resistance, inflammation, and atherosclerosis. *Am J Cardiol*. 2002;90(suppl 5A):27G–33G.
  7. Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care*. 2004;27:1496–1504.
  8. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL, for The Pioglitazone 027 Study Group. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther*. 2000;22:1395–1409.
  9. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial [erratum appears in *JAMA*. 2000;284:1384]. *JAMA*. 2000;283:1695–1702.
  10. Hayashi Y, Miyachi N, Takeuchi T, et al. Clinical evaluation of pioglitazone in patients with type 2 diabetes using alpha-glucosidase inhibitor and examination of its efficacy profile. *Diabetes Obes Metab*. 2003;5:58–65.
  11. Herz M, Johns D, Reviriego J, et al. A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naïve patients with type 2 diabetes mellitus. *Clin Ther*. 2003;25:1074–1095.
  12. Jones TA, Sautter M, Van Gaal LF, Jones NP. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. *Diabetes Obes Metab*. 2003;5:163–170.
  13. Kipnes MS, Krosnick A, Rendell MS, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med*. 2001;111:10–17.
  14. Miyazaki Y, Matsuda M, DeFronzo RA. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. *Diabetes Care*. 2002;25:517–523.
  15. Miyazaki Y, Glass L, Triplitt C, et al. Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in type II diabetic patients. *Diabetologia*. 2001;44:2210–2219.
  16. Miyazaki Y, Mahankali A, Matsuda M, et al. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care*. 2001;24:710–719.
  17. Nolan JJ, Jones NP, Patwardhan R, Deacon LF. Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus. *Diabet Med*. 2000;17:287–294.
  18. Patel J, Anderson RJ, Rappaport EB. Rosiglitazone monotherapy improves glycaemic control in patients with type 2 diabetes: a twelve-week, randomized, placebo-controlled study. *Diabetes Obes Metab*. 1999;1:165–172.
  19. Phillips LS, Grunberger G, Miller E, Patwardhan R, Rappaport EB, Salzman A, for the Rosiglitazone Clinical Trials Study Group. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2001;24:308–315.
  20. Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J, for the Rosiglitazone Clinical Trials Study Group. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care*. 2001;24:1226–1232.
  21. Raskin P, Rappaport EB, Cole ST, Yan Y, Patwardhan R, Freed MI. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. *Diabetologia*. 2000;43:278–284.
  22. Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Robertson KE, the Pioglitazone 026 Study Group. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. *Coron Artery Dis*. 2001;12:413–423.
  23. Rosenstock J, Einhorn D, Hershon K, Glazer NB, Yu S, the Pioglitazone 014 Study Group. Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin therapy. *Int J Clin Pract*. 2002;56:251–257.
  24. Scherbaum WA, Goke B, the German Pioglitazone Study Group. Metabolic efficacy and safety of once-daily pioglitazone monotherapy in patients with type 2 diabetes: a double-blind, placebo-controlled study. *Horm Metab Res*. 2002;34:589–595.
  25. St. John Sutton M, Rendell M, Dandona P, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycaemic control in patients with type 2 diabetes. *Diabetes Care*. 2002;25:2058–2064.
  26. Vongthavaravat V, Wajchenberg BL, Waitman JN, et al., the 125 Study Group. An international study of the effects of rosiglitazone plus sulphonylurea in patients with type 2 diabetes. *Curr Med Res Opin*. 2002;18:456–461.
  27. Wolffenbuttel BR, Gomis R, Squatrito S, Jones NP, Patwardhan RN. Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in Type 2 diabetic patients. *Diabet Med*. 2000;17:40–47.
  28. Boyle PJ, King AB, Olansky L, et al. Effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus: a retrospective review of randomly selected medical records. *Clin Ther*. 2002;24:378–396.
  29. Davidson PC, Sabbah HT, Steed RD, Richardson P, Robertson DG, Bode BW. Pioglitazone versus rosiglitazone therapy in randomized follow-up in patients previously treated with troglitazone [Abstract]. *Diabetes*. 2001;50(suppl 2):A109.
  30. Faiman MR, Faiman GH, Mehta AE. Effect of pioglitazone (Actos) vs rosiglitazone (Avandia) on lipid profiles. Presented at the American Association of Clinical Endocrinologists; May 2–4, 2001; San Antonio, TX.
  31. Gegick CG, Altheimer MD. Thiazolidinediones: comparison of long-term effects on glycemic control and cardiovascular risk factors. *Curr Med Res Opin*. 2004;20:919–930.
  32. Gegick CG, Altheimer MD. Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. *Endocr Pract*. 2001;7:162–169.
  33. Goldberg RB, Kendall DM, Deeg MA, et al., for the GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care*. 2005;28:1547–1554.
  34. Khan MA, St. Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care*. 2002;25:708–711.
  35. King AB. A comparison in a clinical setting of the efficacy and side effects of three thiazolidinediones [Letter]. *Diabetes Care*. 2000;23:557.
  36. LaCivita KA, Villarreal G. Differences in lipid profiles of patients given rosiglitazone followed by pioglitazone. *Curr Med Res Opin*. 2002;18:363–370.
  37. Lewin AJ, Kipnes MS, Meneghini LF, et al., for the Simvastatin/Thiazolidinedione Study Group. Effects of simvastatin on the lipid profile and attainment of low-density lipoprotein cholesterol goals when added to thiazolidinedione therapy in patients with type 2 diabetes mellitus: a multicenter, randomized, double-blind, placebo-controlled trial. *Clin Ther*. 2004;26:379–389.
  38. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
  39. Chu NV, Kong AP, Kim DD, et al. Differential effects of metformin and troglitazone on cardiovascular risk factors in patients with type 2 diabetes [erratum appears in *Diabetes Care*. 2002;25:947.] *Diabetes Care*. 2002;25:542–549.
  40. Freed MI, Ratner R, Marcovina SM, et al., on behalf of the Rosiglitazone Study 108 Investigators. Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. *Am J Cardiol*. 2002;90:947–952.
  41. Ghazzi MN, Perez JE, Antonucci TK, et al. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. The Troglitazone Study Group. *Diabetes*. 1997;46:433–439.
  42. King AB, Armstrong D. Comparison of the glucose and lipid effects of

- rosiglitazone (ROS) and pioglitazone (PIO) following conversion from troglitazone (TRO) treatment [Abstract]. *Diabetes*. 2001;50(suppl 2): A120–121.
43. Tack CJ, Smits P, Demacker PN, Stalenhoef AF. Troglitazone decreases the proportion of small, dense LDL and increases the resistance of LDL to oxidation in obese subjects. *Diabetes Care*. 1998;21:796–799.
44. Winkler K, Konrad T, Fullert S, et al. Pioglitazone reduces atherogenic dense LDL particles in nondiabetic patients with arterial hypertension: a double-blind, placebo-controlled study. *Diabetes Care*. 2003;26:2588–2594.
45. Rosenstock J, Raskin P. Hypertension in diabetes mellitus. *Cardiol Clin*. 1988;6:547–560.
46. Simonson DC. Etiology and prevalence of hypertension in diabetic patients. *Diabetes Care*. 1988;11:821–827.
47. Ogihara T, Rakugi H, Ikegami H, Mikami H, Masuo K. Enhancement of insulin sensitivity by troglitazone lowers blood pressure in diabetic hypertensives. *Am J Hypertens*. 1995;8:316–320.
48. Sung BH, Izzo JL Jr, Dandona P, Wilson MF. Vasodilatory effects of troglitazone improve blood pressure at rest during mental stress in type 2 diabetes mellitus. *Hypertension*. 1999;34:83–88.
49. Walker AB, Chattington PD, Buckingham RE, Williams G. The thiazolidinedione rosiglitazone (BRL-49653) lowers blood pressure and protects against impairment of endothelial function in Zucker fatty rats. *Diabetes*. 1999;48:1448–1453.